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# Process modelling, simulation and technoeconomic optimisation for continuous pharmaceutical manufacturing of (*S*)-warfarin

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## Abstract

Continuous pharmaceutical manufacturing (CPM) has the potential to attain several technical and operational economic benefits compared to the currently prevalent batch production paradigm. Despite the variety of demonstrated continuous flow syntheses of active pharmaceutical ingredients (APIs), the limited number of cost-effective continuous separations is a bottleneck to end-to-end CPM. Establishing promising APIs for integrated CPM is paramount. (*S*)-Warfarin is an anticoagulant API whose continuous flow synthesis features a single reaction with high enantiomeric selectivity followed by liquid-liquid extraction (LLE). This work describes the steady-state process modelling and technoeconomic optimisation for the upstream CPM of (*S*)-warfarin, implementing reactor design and LLE solvent comparison for purification. Ethyl acetate, isopropyl acetate, isobutyl acetate, 1-heptanol, 1-octanol and heptane are candidate LLE solvents. Reported reaction conversions and computed LLE efficiencies allow mass balance calculation and total cost estimation to establish promising LLE solvents. The nonlinear optimisation problem is formulated for total cost minimisation. Liquid-liquid phase equilibria, API phase compositions and solubilities for LLE design are implemented via surrogate polynomials based on extensive UNIFAC modelling; API recovery rates are calculated via detailed mass transfer correlations. The methodology used here screens optimum process configurations to achieve a technoeconomically optimal design for a continuous (*S*)-warfarin manufacturing plant.

**Keywords:** Continuous Pharmaceutical Manufacturing (CPM), (*S*)-warfarin.

## 1. Introduction

Continuous pharmaceutical manufacturing (CPM) is a key area of green chemistry research with the potential for significant technical, operational and economic benefits over currently prevalent batch manufacturing methods (Koenig and Dillon, 2017). Despite the numerous demonstrations of continuous flow syntheses (Britton and Raston, 2017) towards active pharmaceutical ingredients (APIs), including end-to-end production campaigns (Adamo et al., 2016), only certain synthetic routes benefit from continuous operation (Hartman et al., 2011) and the lack of demonstrated continuous purification and separation methods integrated in CPM plants is an important obstacle (Bana et al., 2017). Establishing promising APIs for CPM application and screening for those with the highest likelihood of success is imperative for the elucidation of potential process configurations and successful implementation of continuous manufacturing routes (Teoh et al., 2015), and process modelling is critical in performance evaluation.

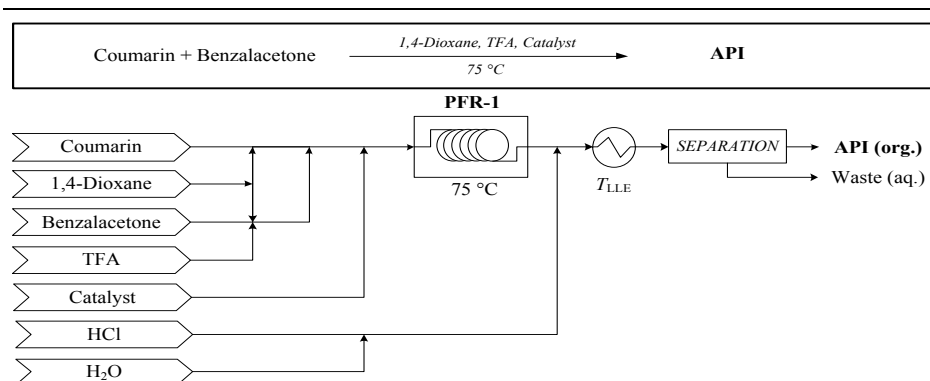
(*S*)-Warfarin is an anticoagulant API, commonly known as Coumadin<sup>®</sup>, commonly used for the treatment of deep vein thrombosis and pulmonary embolism (Porter, 2015). The continuous flow synthesis of (*S*)-warfarin features a single reaction and subsequent liquid-liquid extraction (LLE) process (Porta et al., 2015). Comparison of different conceptual separation process alternatives is essential for establishing cost-effective, materially efficient designs for upstream CPM configurations. Screening of candidate continuous LLE configurations for CPM of this API has yet to be conducted; process modelling, simulation and optimisation of continuous separation processes are valid alternatives to laborious experimental efforts for rapid design space investigation to elucidate technically feasible and economically viable processes (Jolliffe et al., 2018).

Here, we implement steady-state process modelling and nonlinear optimisation for the upstream CPM of (*S*)-warfarin, including continuous flow synthesis and LLE. Flowsheet development based upon the published continuous synthetic route and a conceptual continuous LLE process are presented, comparing various separation solvents. Thermodynamic models for liquid-liquid phase composition and API solubility prediction in non-ideal, multicomponent mixtures for LLE design are described. Nonlinear optimisation problem formulation for total cost minimisation are presented. Minimum total costs, optimal API recoveries and material efficiencies for different process configurations are compared to establish promising LLE solvents.

## 2. Process Modelling and Nonlinear Optimisation

### 2.1 Continuous Flow Synthesis and Process Flowsheet

The flowsheet for the CPM of (*S*)-warfarin (API) is shown in Fig. 1 (Porta et al., 2015). The continuous flow synthesis of the API features the nucleophilic addition of 4-hydroxy-coumarin with benzalacetone in the presence of trifluoroacetic acid (TFA) and a chiral amine catalyst at 75 °C in 1,4-dioxane, with a reported conversion of 61%. Aqueous HCl (10% w/w) is added to the reactor effluent before entering the LLE unit. Upon addition of the candidate LLE solvent, the process forms an organic (product) phase containing recovered API and an aqueous (waste) phase, between which API partitions. Several candidate separation solvents are compared for continuous LLE: ethyl acetate (EtOAc), isopropyl acetate (iPrOAc), isobutyl acetate (iBuOAc), 1-heptanol (HepOH), 1-octanol (OcOH) and *n*-heptane (nHep), as per (Alder et al. (2016).



**Figure 1:** Process flowsheet for continuous (*S*)-warfarin production (Porta et al., 2015).

## 2.2 Separation Design and Thermodynamic Modelling

Continuous separation (LLE) processes are modelled as single-stage mixer-settlers at  $T_{\text{LLE}} = 20, 40, 60$  °C and solvent feed rates  $r = 1\text{--}4$  (mass basis). The rate of API recovery,  $\dot{f}$ , is described by Eq. 1.  $K$  is the overall mass transfer coefficient,  $a$  is the volume-specific interfacial area,  $V_{\text{LLE}}$  is the tank volume, and  $C^*$  and  $C$  are the theoretical and equilibrium API concentrations in the product phase, respectively.  $k_i$  and  $Sh_i$  are phase mass transfer coefficients and Sherwood numbers, respectively,  $D_{\text{API}}$  is the API diffusivity,  $d_{32}$  is the dispersed phase Sauter mean droplet diameter,  $Sc$  is the Schmidt number,  $Fr$  is the Froude number,  $Eu$  is the Eotvos number,  $\phi$  is the dispersed phase volume fraction,  $Re_i$  is the impeller Reynolds' number,  $d_i$  and  $d_t$  are the impeller and tank diameters, respectively,  $We$  is the Weber number,  $N_i$  is the impeller rotation speed,  $\rho_c$  is the continuous phase density and  $\sigma$  is the interfacial surface tension (Skelland and Moetti, 1990).

$$\dot{f} = KaV_{\text{LLE}}(C^* - C) \quad (1)$$

$$K = (k_c^{-1} + k_d^{-1})^{-1} \quad (2)$$

$$Sh_d = \frac{k_d d_{32}}{D_{\text{API},d}} = 6.6 \quad (3)$$

$$Sh_c = \frac{k_c d_{32}}{D_{\text{API},c}} = 1.25 \cdot 10^{-5} Sc_c^{1/3} Fr_c^{5/12} Eu^{5/4} \phi^{-1/2} Re^{2/3} \left(\frac{d_i}{d_{32}}\right)^2 \left(\frac{d_{32}}{d_t}\right)^{1/2} \quad (4)$$

$$d_{32} = \begin{cases} 0.052 d_i We^{-0.6} \exp 4\phi & , We < 10^3 \\ 0.390 d_i We^{-0.6} & , We > 10^3 \end{cases} \quad (5)$$

$$We = \frac{d_i^3 N_i^2 \rho_c}{\sigma} \quad (6)$$

$$a = \frac{6\phi}{d_{32}} \quad (7)$$

Phase compositions and mixture API solubilities are predicted via the UNIFAC model. LLE stage efficiencies ( $E_{\text{LLE}}$ ) allow calculation of actual product API concentrations from theoretical API concentrations in the product phase.

$$E_{\text{LLE}} = ((Ka\tau_{\text{LLE}})^{-1} + 1)^{-1} \quad (8)$$

## 2.3 Nonlinear Optimisation Formulation

The aim of the optimisation is to minimise the total cost objective function (*Cost*).

$$\min \text{Cost} = \text{CapEx} + \sum_{t=1}^{\tau} \frac{\text{OpEx}}{(1+y)^t} \quad (9)$$

$$\tau_{\text{LLE}} > 0 \quad (10)$$

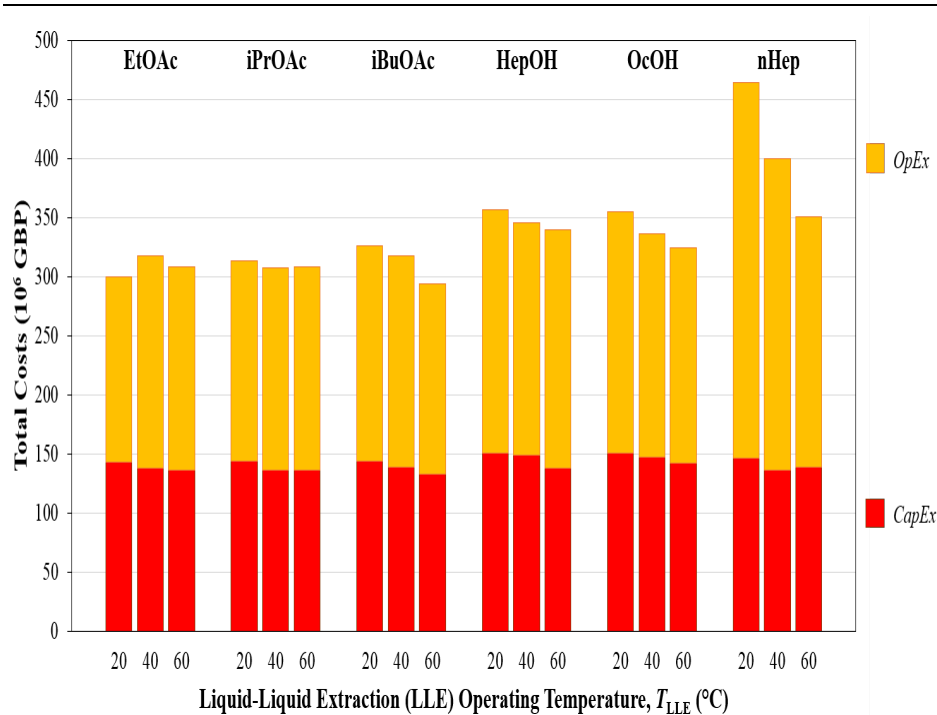
$$1 < r < 4 \quad (11)$$

The discount rate ( $y = 5\%$ ) accounts for inflation and  $\tau$  is the plant lifetime (20 years). Annual operation of 8,040 hours is considered. Optimisation decision variables are the LLE residence time ( $\tau_{\text{LLE}}$ ) and relative solvent feed rate ( $r$ ). Capital (*CapEx*) expenditure includes battery limits installed costs, construction and working capital; operating expenditure (*OpEx*) is the sum of material costs, utilities and waste handling requirements (Schaber et al., 2011). Solvent recovery after LLE is assumed to be 70%; all material requirements are scaled to account for reaction and separation inefficiencies.

### 3. Results and Discussion

Minimum total costs for each LLE solvent and operating temperature are shown in Fig. 2. The LLE solvent with the lowest minimum total costs is iBuOAc ( $293.87 \cdot 10^6$  GBP, 60 °C), followed by EtOAc ( $299.91 \cdot 10^6$  GBP, 20 °C) and iPrOAc ( $299.93 \cdot 10^6$  GBP, 60 °C). These solvents perform comparably due to their similar molecular structures and polarities, inducing similar phase compositions and thus comparable API recoveries. This effect is also observed for HepOH and OcOH, which attain the next lowest total costs ( $339.43 \cdot 10^6$  GBP and  $324.54 \cdot 10^6$  GBP, respectively) both operating at  $T_{LLE} = 60$  °C. The poorest performance is attained via nHep (min cost =  $350.52 \cdot 10^6$  GBP, 60 °C).

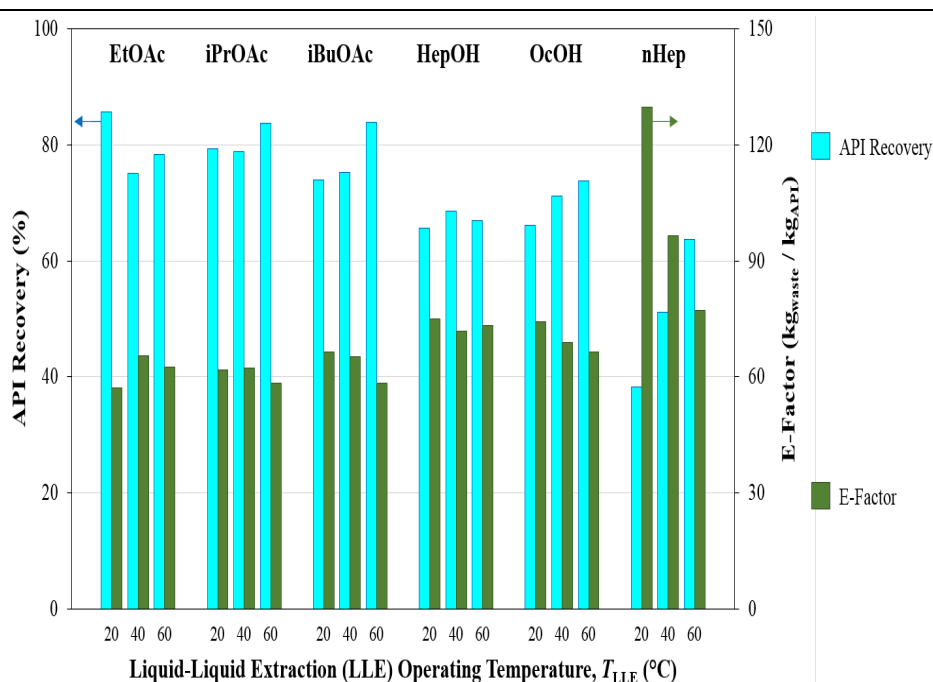
For most cases, increasing operating temperature leads to lower total costs due to the enhanced mass transfer (recovery) rates of API into the product phase, which requires shorter LLE tank residence times (lower *CapEx*) and material requirements (lower *OpEx*) to meet the plant capacity of 100 kg per annum. When nHep is implemented as a separation solvent, *OpEx* is significantly higher for all LLE operating temperatures (20, 40, 60 °C) considered, due to the low API recoveries attainable in comparison to other separation solvents considered in this work (Fig. 3). In all process configurations, the solvent feed rate ( $r$ ) is pushed to its lower bound ( $= 1$ ). The solvent feed rate and its assumed recovery following LLE directly affects materials and waste treatment costs (key *OpEx* components). The sensitivity of total cost minima to varying solvent recovery can be readily compared using the methodological framework described here.



**Figure 2:** Minimum total costs attainable for different continuous LLE configurations.

Attainable  $E$ -factors for all processes vary between 57–127; whilst these values are high in comparison to other manufacturing sectors ( $E < 0.1$  for oil and gas processing), they are reasonable for pharmaceutical manufacturing processes (Roschangar et al., 2015). The  $E$ -factor variations are directly related to corresponding API recoveries; as API recovery increases, material requirements and waste (and thus the  $E$ -factor) decrease. Implementing the process configuration with the lowest total costs (iBuOAc, 60 °C) attains  $E = 58.4$ , which is very low in comparison to other configurations in this work.

The described framework can be used to perform sensitivity analyses with respect to economic data (e.g. varying material prices, rates of interest for inflation) and other operational assumptions (e.g. achieved solvent recovery). It also allows the investigation of the effect of scaling plant capacity on total cost components and  $E$ -factors, an essential consideration during process development. Candidate separation solvents investigated for application here have been selected based upon their suitability for LLE (i.e. exhibit rapid phase splitting with the process mixture and are considered suitable with respect to detailed EHS criteria). (S)-Warfarin is available in both liquid (dispersion) and solid (tablet) formulations, and thus consideration of crystallisation and downstream processing following the upstream CPM considered in this work. Consideration of the effects of LLE solvent choices and resulting API recoveries and purities in the organic product phase on the requirement for additional purification prior to further processing will aid LLE solvent selection. The methodology described in this work can be implemented for other APIs requiring continuous LLE, provided that kinetic and thermodynamic data are available for modelling and total cost minimisation.



**Figure 3:** API recoveries and E-factors corresponding to total cost minima.

#### 4. Conclusions

This paper presents the systematic evaluation of six candidate separation solvents for the continuous liquid-liquid extraction (LLE) of (*S*)-warfarin following the experimentally demonstrated continuous flow synthesis (Porta et al., 2015). Comparison of minimum total costs via nonlinear optimisation with LLE solvent feed rate and tank residence time as decision variables establish promising candidate LLE solvents for the CPM of (*S*)-warfarin. Isobutyl acetate (iBuOAc) emerges as a promising candidate LLE solvent, attaining the lowest minimum total costs of  $293.87 \cdot 10^6$  GBP and a reasonable E-factor of 58.4, followed by ethyl acetate and isobutyl acetate. The considered alcohols (1-heptanol and 1-octanol) and *n*-heptane attain inferior performance (higher total costs) due to lower maximum (theoretical) API recoveries estimated by the UNIFAC method.

The technoeconomic and environmental impact analyses presented in this work can inform the future design of CPM processes for this societally important API. Consideration of wider operating parameter sets and additional LLE solvents can be performed by adapting the existing framework, given the availability of required thermodynamic data and physical properties. Sensitivity analyses with respect to varying performance assumptions (e.g. varied attainable reaction and separation efficiencies upon scale up) and economic considerations (available solvent recovery, interest rates etc.) can be implemented within the framework and will add robustness to the presented results. Consideration of carrier and separation solvent combinations on subsequent upstream (e.g. crystallisation) and downstream (product formulation) unit operations is essential for successful implementation of a fully continuous process.

#### 5. Acknowledgements

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